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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/518,842	03/03/00	JASPERS S	96-41D1

HM12/0717

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EXAMINER	
BUNNER, B	
ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 07/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/518,842	Applicant(s) JASPERS ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-15* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647, Examiner Bridget E. Bunner.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-5, drawn to a protein in Paper No. 5 (19 June 2001) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5 (19 June 2001).

Claims 1-5 are under consideration in the instant application.

Information Disclosure Statement

1. The information disclosure statement filed 23 January 2001 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

4. The disclosure is objected to because of the following informalities:

4a. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. A statement reading "This is a divisional of U.S. Application No. 08/991,890, filed December 12, 1997, now Patent No. 6,114,307, which is related to U.S. Provisional Application No. 60/033,003, filed December 16, 1996" should be entered.

4b. The use of the trademarks TISSUE-TEK, NOVEX, and CARBOPAC have been noted in this application (for example, see pages 42, 46, 48-49). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "ZINS1 POLYPEPTIDE COMPOSITION FOR STIMULATING PANCREATIC ISLET CELL GROWTH".

Appropriate correction is required.

Claim Objections

5. Claims 4-5 are objected to because of the following informalities:

5a. The term "disulfide associating" in claims 4-5 should be reworded to read "disulfide association".

5b. Regarding claims 4-5, the word "the" should be inserted directly in front of the term "amino acid sequence". (Note, there should be two insertions per claim.)

5c. The word "a" or "the" should be inserted directly in front of the term "residue" in line 3 of claim 5.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims read on a product of nature in that the claimed polynucleotide is not "isolated". Amending the claims to read "isolated" would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5 recite a protein comprising an amino acid sequence from residue 26 to residues 48, 49, 50, 110, or 114 of SEQ ID NO: 2. The claims are also directed to a protein comprising an amino acid sequence from residue 115 to residue 139 of SEQ ID NO: 2.

The specification discloses that protein of the instant application, zins1, comprises "a disulfide bonded B chain and A chain, wherein the B chain comprises the amino acid sequence of SEQ ID NO: 2 from residue 26 to at least amino acid residue 43 and wherein the A chain comprises the amino acid sequence of SEQ ID NO: 2 from amino acid residue 115 to residue 139 based on sequence alignment and analyses" (pg 12, lines 25-32). However, the specification does not teach any structural or functional characteristics of polypeptide fragments comprising amino acids 26-48, 26-49, 26-50, 26-110, 26-114, and 115-139 of SEQ ID NO: 2. The specification teaches that the "present inventors have isolated and purified the polypeptide from the medium conditioned by host cells co-expressing a first DNA construct comprising the sequence of SEQ ID NO: 1 from nucleotide 1 to nucleotide 420 with a second DNA construct encoding for endoprotease PC3" (pg 12, lines 32-36, pg 13, line 1). Several bands are sequenced from various clones, particularly bands of 14.5, 9.0, 8.0, and 3.5 kDa from clone zins1C/PC3#9. The specification discloses that the first three bands *start* with amino acid residues 26-32 of SEQ ID NO: 2 which appear to be the N-terminus of the mature zins1 protein (B-chain). The 3.5 kDa band *starts* with amino acid residues 115-121 of SEQ ID NO: 2, representing the N-terminus of

the A-chain (pg 38, lines 3-22). However, the specification does not teach the entire length of the amino acid sequence of the isolated bands. Therefore, the skilled artisan would not know if the mature zins1 protein, specific fragments, or the zins1 protein with deletions is being encoded by the clones. Undo experimentation would be required of one skilled in the art to determine the amino acid sequences of the zins1 polypeptide bands isolated from the zins1C/PC3 and zins1N/PC3 clones.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not

adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the protein derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7a. Claims 4-5 are indefinite because it is not clear how an isolated protein comprises a "first polypeptide" and a "second polypeptide". For example, is the protein claimed in the instant

application a fusion protein? Are the "first polypeptide" and "second polypeptide" only specific residues within a larger protein being claimed? Or, is the claimed protein part of a protein that has deletions?

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 rejected under 35 U.S.C. 102(b) as being anticipated by Chassin et al. (Genomics 29: 465-470, 1995).

Chassin et al. teaches an isolated protein comprising amino acid residues 26-48, 26-49, 26-50, 26-110, 26-114, and 115-139 of SEQ ID NO: 2 of the instant application (see pg 467, Figure 1; see also sequence alignment attached to this Office Action as Appendix A).

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Koman et al. U.S. patent 5,910,480

Bellet et al. J Clin Endocrinol Metab 82: 3169-3172, 1997.

Koman et al. WO 95/34653

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

BEB
Art Unit 1647
July 11, 2001

Appendix A

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RESULT   1
INL4_HUMAN
ID   INL4_HUMAN     STANDARD;      PRT;   139 AA.
AC   Q14641;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   30-MAY-2000 (Rel. 39, Last annotation update)
DE   EARLY PLACENTA INSULIN-LIKE PEPTIDE PRECURSOR (EPIL) (PLACENTIN)
DE   (INSULIN-LIKE PEPTIDE 4).
GN   INSL4.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Placenta;
RX   MEDLINE=96115599; PubMed=8666396;
RA   Chassin D., Laurent A., Janneau J.-L., Berger R., Bellet D.;
RT   "Cloning of a new member of the insulin gene superfamily (INSL4)
RT   expressed in human placenta.";
RL   Genomics 29:465-470(1995).
RN   [2]
RP   PROCESSING.
RX   MEDLINE=97430657; PubMed=9284764;
RA   Bellet D., Lavaissiere L., Mock P., Laurent A., Sabourin J.C.,
RA   Bedossa P., Le Bouteiller P., Frydman R., Troalen F., Bidart J.M.;
RT   "Identification of pro-EPIL and EPIL peptides translated from
RT   insulin-like 4 (INSL4) mRNA in human placenta.";
RL   J. Clin. Endocrinol. Metab. 82:3169-3172(1997).
RN   [3]
RP   TISSUE SPECIFICITY.
RX   MEDLINE=98411035; PubMed=9740319;
RA   Laurent A., Rouillac C., Delezoide A.L., Giovangrandi Y., Vekemans M.,
RA   Bellet D., Abitbol M., Vidaud M.;
RT   "Insulin-like 4 (INSL4) gene expression in human embryonic and
RT   trophoblastic tissues.";
RL   Mol. Reprod. Dev. 51:123-129(1998).
CC   -!- FUNCTION: MAY PLAY AN IMPORTANT ROLE IN TROPHOBLAST DEVELOPMENT
CC       AND IN THE REGULATION OF BONE FORMATION.
CC   -!- TISSUE SPECIFICITY: EXPRESSED IN PLACENTA, UTERUS AND IN FETAL
CC       PERICHONDIRUM.
CC   -!- DEVELOPMENTAL STAGE: HIGHLY EXPRESSED IN THE EARLY PLACENTA.
CC       EXPRESSION OF EPIL PEPTIDES IN THE VILLOUS CYTOTROPHOBLAST IS
CC       DIFFERENT FROM THAT DISPLAYED BY THE SYNCYTIOTROPHOBLAST. IN FETAL
CC       TISSUES IT WAS IDENTIFIED IN THE PERICHONDRIUM OF ALL FOUR LIMBS,
CC       VERTEBRAE, AND RIBS. IT WAS ABUNDANT IN INTERBONE LIGAMENTS.
CC   -!- SIMILARITY: BELONGS TO THE INSULIN/IGF/RELAXIN FAMILY.
CC   ----------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ----------------------------------------------------------------------
DR   EMBL; L34838; AAB08516.1; -.
DR   MIM; 600910; -.
DR   InterPro; IPR000739; -.
DR   PROSITE; PS00262; INSULIN; 1.
KW   Insulin family; Hormone; Signal.
FT   SIGNAL       1     17       POTENTIAL.
FT   CHAIN       18    139       EARLY PLACENTA INSULIN-LIKE PEPTIDE.
FT   CHAIN       18     58       EARLY PLACENTA INSULIN-LIKE PEPTIDE B
FT                               CHAIN.
FT   PROPEP      59    109       C PEPTIDE.
FT   CHAIN      110    139       EARLY PLACENTA INSULIN-LIKE PEPTIDE A
FT                               CHAIN.
FT   DISULFID    31    125       INTERCHAIN (BY SIMILARITY).
FT   DISULFID    43    138       INTERCHAIN (BY SIMILARITY).
FT   DISULFID   124    129       BY SIMILARITY.
SQ   SEQUENCE   139 AA;  15445 MW;  47FB61F6F86C1342 CRC64;

  Query Match          100.0%;  Score 739;  DB 1;  Length 139;
  Best Local Similarity  100.0%;  Pred. No. 1.8e-67;
  Matches  139;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1 MASLFRSYLPAIWLLLSQLLRESLAAELRGCGPRFGKHLLSYCPMPEKTFTTTPGGWLLE 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MASLFRSYLPAIWLLLSQLLRESLAAELRGCGPRFGKHLLSYCPMPEKTFTTTPGGWLLE 60

Qy      61 SGRPKEMVSTSNNKDGQALGTTSEFIPNLSPELKKPLSEGQPSLKKIILSRKKRSGRHRF 120
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 SGRPKEMVSTSNNKDGQALGTTSEFIPNLSPELKKPLSEGQPSLKKIILSRKKRSGRHRF 120

Qy     121 DPFCCEVICDDGTSVKLCT 139
           ||||||||||||||||||||
Db     121 DPFCCEVICDDGTSVKLCT 139
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